Osteoarthritis and Cartilage (2009) **17,** 1327–1332

doi:10.1016/j.joca.2009.03.020

Osteoarthritis and Cartilage

International Cartilage Repair Society

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Investigation of the frictional response of osteoarthritic human tibiofemoral joints and the potential beneficial tribological effect of healthy synovial fluid

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Summary

Objective: This study tests the hypothesis that the natural progression of osteoarthritis (OA) in human joints leads to an increase in the friction coefficient. This hypothesis is based on the expectation that the wear observed in OA may be exacerbated by higher friction coefficients. A corollary hypothesis is that healthy synovial fluid (SF) may help mitigate the increase in the friction coefficient in diseased joints.

Design: The friction coefficient of human tibiofemoral joints with varying degrees of OA was measured in healthy bovine SF and physiological buffered saline (PBS). Two testing configurations were adopted, one that promotes sustained cartilage interstitial fluid pressurization to investigate the effectiveness of this mechanism with advancing OA, and another that allows interstitial fluid pressure to subside to investigate the effectiveness of boundary lubrication.

Results: Seven specimens were visually staged to be normal or mildly degenerated (stages ≤ 2 on a scale of 1 to 4) and nine others had progressive degeneration (stages > 2 and ≤ 3). No statistical differences were found in the friction coefficient with increasing OA, whether in migrating or stationary contact area configurations; however, the friction coefficient was significantly lower in SF than PBS in both configurations.

Conclusions: The friction coefficient of human tibiofemoral cartilage does not necessarily increase with naturally increasing OA, for visual stages ranging from 1 to 3. This outcome may be explained by the fact that interstitial fluid pressurization is not necessarily defeated by advancing degeneration. This study also demonstrates that healthy SF decreases the friction coefficient of OA joints relative to PBS.

Key words: Cartilage friction, Osteoarthritis, Synovial fluid.

Introduction

It is noteworthy that the friction coefficient of osteoarthritic human joints has not been reported previously. Prior *in vitro* and *in vivo* friction studies have induced degradation of bovine articular cartilage by enzymatic action[1–5] or by mechanical abrasion[6,7] as a means to simulate osteoarthritis (OA), generally reporting that the friction coefficient increases with degradation. Gene knockout studies have examined the frictional response of animal joints lacking expression of lubricin/superficial zone protein by PRG4[8,9], also showing an increase in friction and wear. In humans, mutations in the PRG4 gene have been shown to cause the autosomal recessive disorder camptodactyly arthropathy-coxa vara-pericarditis syndrome (CACP), which is accompanied by precocious joint failure[10]. On the basis of these findings we hypothesize that the natural progression of OA in human joints leads to an increase in the friction coefficient. This hypothesis is based on the expectation that the wear observed in OA may be exacerbated by higher friction coefficients. Though the prior literature appears to support this hypothesis, it remains to be tested directly.

There are two dominant modes of lubrication in articular cartilage: lubrication by interstitial fluid pressurization[11–14], and boundary lubrication by synovial fluid (SF)[15–18]. In our recent study, we have shown that lubrication by interstitial fluid pressurization is normally much more effective than boundary lubrication by SF, as it can reduce the friction coefficient by a factor of ~60 relative to equilibrium conditions when interstitial fluid pressurization has subsided; in contrast, SF reduced the friction coefficient by a factor of ~1.5 relative to saline[18], although other studies have exhibited slightly higher[17] or lower[12] relative reductions.

A potential mechanism for explaining a rise in friction may be the loss of interstitial fluid pressurization with increasing OA, as suggested by studies of enzymatically degraded bovine articular cartilage[3,19]. It is also known that OA compromises the rheological properties of SF[20–22], and some studies also suggest that it may also decrease the concentration of boundary lubricants[5,23–25]. A corollary hypothesis of this study is that healthy SF may help mitigate the increase in the friction coefficient of OA joints.

In this study these hypotheses are tested by measuring the friction coefficient of human tibiofemoral joints with varying degrees of OA progression, in healthy bovine SF or physiological buffered saline (PBS). Two testing

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Received 8 July 2008; revision accepted 26 March 2009.

Table I
Visual staging for osteoarthritis[27]

Stage	Cartilage state	Description
1	Normal	Smooth, shiny, intact surface
2	Early degeneration	Matted, dull surface; mild fibrillation
3	Progressive degeneration	Pitting with or without fibrillation, fissures, clefts, blisters
4	End-stage degeneration	Bone eburnation, osteophytes

configurations are adopted, one that promotes sustained interstitial fluid pressurization to investigate the effectiveness of this mechanism with advancing OA, and another that allows interstitial fluid pressure to subside to investigate the effectiveness of boundary lubrication.

Methods

As described in our earlier study[18], interstitial fluid pressurization can be sustained for long durations if the articular contact area migrates continuously over one or both of the contacting cartilage layers[26]. This migrating contact area (MCA) configuration can be achieved, for example, by sliding the femoral condyle over the tibial plateau. Conversely, interstitial fluid pressurization subsides when the contact area remains stationary over the cartilage layer, since the pressurized interstitial fluid eventually flows away from the underlying tissue; this stationary contact area (SCA) configuration can be achieved, for example, by sliding a cylindrical cartilage plug against a flat glass slide.

SPECIMEN PREPARATION

Eight fresh frozen human knee joints (average age 70 y.o., ranging from 50 to 94; four females and four males) were obtained from a tissue bank and stored at -20°C for less than 1 month before dissection. Each joint was dissected to expose the articular cartilage on the distal femur and proximal tibia; the patella and soft tissues, including ligaments and menisci, were removed. A band saw was used to separate the lateral and medial sides along the mid-sagittal plane, and to isolate the needed portions of the distal femoral condyle and tibial plateau. Utmost care was used during specimen preparation to avoid scratching or damaging the articular cartilage. Each joint yielded medial and lateral tibiofemoral pairs which were treated as separate samples, resulting in $n = 16$ samples.

Synovial fluid was pooled from 10 adult bovine wrist joints and mixed on an orbital shaker. Only samples that were free of blood contamination were used, as assessed visually. SF was stored at -20°C between testing sessions and used within 2 months of collection.

STAGING FOR OSTEOARTHRITIS

A visual staging for OA was performed for each sample, using a common scheme[27], with stage 1 representing normal tissue and stage 4 representing

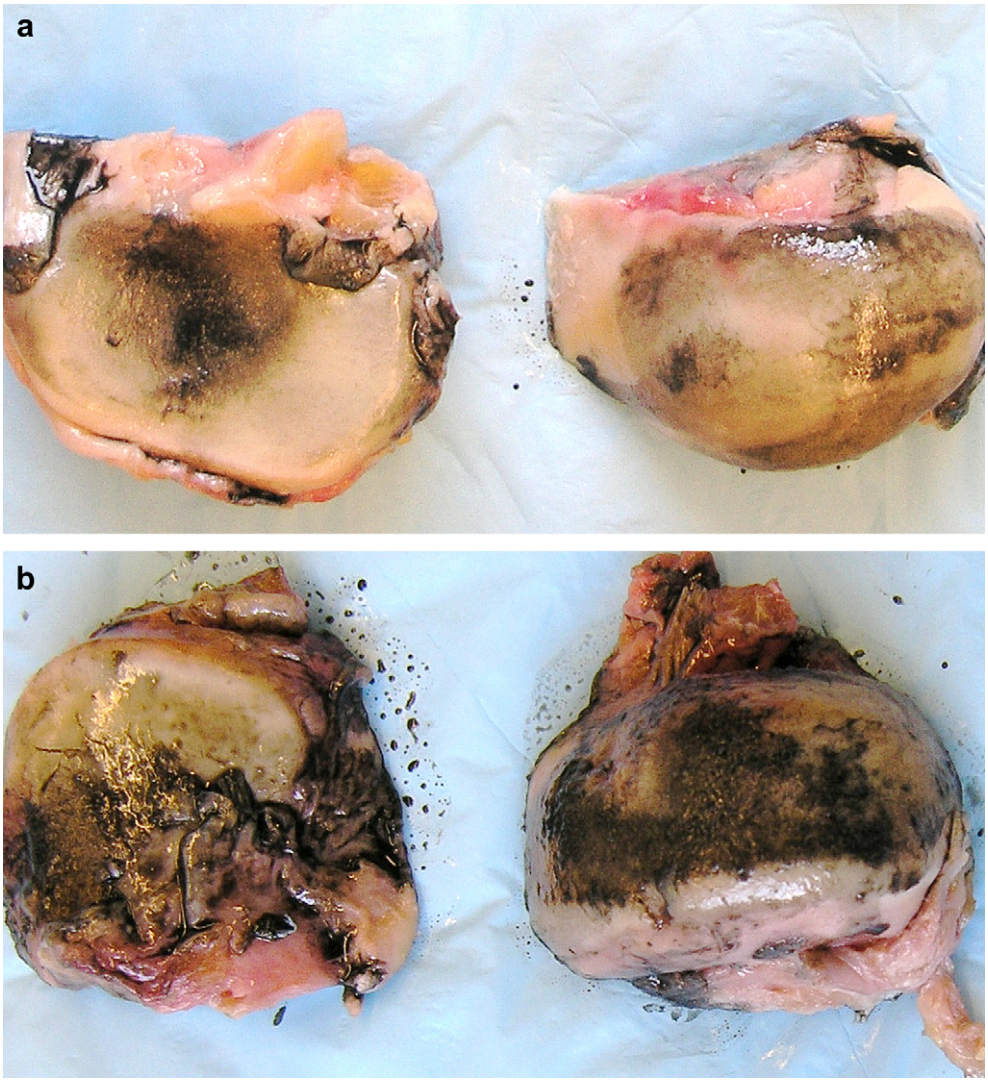

Fig. 1. Representative joints with (a) visual stage 1.2 OA and (b) visual stage 3 OA.

Table II
Mean ± standard deviations of the mechanical and biochemical properties of all specimens (n = 16). For each property, the means and standard deviations of values below (n = 8) and above (n = 8) its respective median are also provided. For the modulus, GAG and collagen content, values above the median represent less-OA, whereas values below it represent more-OA; the reverse applies to the water content

Property	All specimens	Less-OA	More-OA
Young's modulus (MPa)	0.64 ± 0.49	1.12 ± 0.16	0.24 ± 0.20
GAG content (% w.w.)	1.5 ± 0.8	2.1 ± 0.8	1.0 ± 0.3
Collagen content (% w.w.)	17.0 ± 3.0	19.5 ± 1.6	14.6 ± 1.7
Water content (% w.w.)	80.5 ± 3.9	77.6 ± 2.9	83.0 ± 2.1

the most advanced stage of degeneration (Table I). This visual staging was facilitated by staining the articular surfaces with India ink, and based on the most degraded region of that sample. The score for each sample was averaged from three blind reviews. India ink was rinsed away with PBS prior to friction testing.

In addition to this visual assessment, basic measures of mechanical properties and biochemical composition of cartilage from these samples were also used to assess the relative degree of tissue degradation among the various samples, as described below.

FRICTION TESTS

The friction testing protocol follows that described in our recent study[18] and briefly summarized here. Each sample was subjected to MCA and SCA tests in PBS and SF, for a total of four tests per sample. First, the femoral condyle was reciprocally translated against the tibial plateau (±1 mm/s) under a constant load (6.27 N) for 900 s, in a bath of PBS containing protease inhibitors (PI, Complete Cocktail Tablet, Roche Applied Science, Indianapolis, IN) (MCA−PBS test). Based on preliminary measurements of the contact area using pressure-sensitive film, the resulting contact stress was ~0.2 MPa. The sample was subsequently allowed to recover for 20 min, followed by a second test in the same configuration, using SF as a lubricant (MCA−SF). Due to the limited availability of SF, only the contact region was covered with SF, whereas the non-contacting regions were covered with gauze soaked in PBS. A continuous supply of SF was maintained by adding 1 ml to the contact region for every 3 min of testing. As shown previously[18] these MCA tests produce a friction coefficient that decreases slightly in the first few minutes and remains nearly constant for the remaining duration of the test; a friction coefficient μ_{MCA} was determined by averaging measurements from the last 600 s.

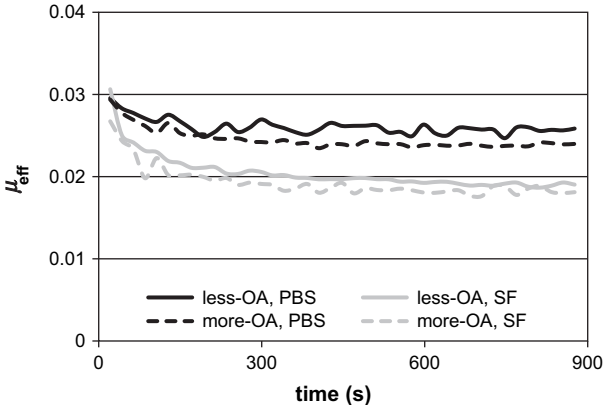

Fig. 2. Friction coefficient μ_{eff} in the MCA configuration. Average responses are shown, as a function of visual stage of OA and lubricant used. For each sample, the value of μ_{eff} was averaged over the last 600 s to produce μ_{MCA}. Means and standard deviations for μ_{MCA} are provided in Table III, and statistical differences in Table IV.

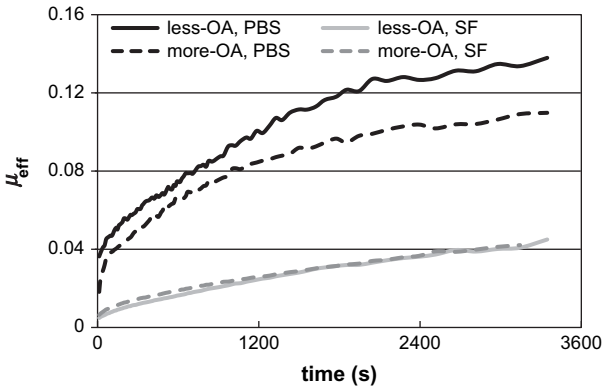

Fig. 3. Friction coefficient μ_{eff} in the SCA configuration. Average responses are shown, as a function of visual stage of OA and lubricant used. For each sample, the initial value of μ_{eff} is also its minimum value μ_{min}, while the final value is taken as a close approximation to the equilibrium value μ_{eq}. Means and standard deviations for μ_{min} and μ_{eq} are provided in Table III, and statistical differences in Table IV.

At the completion of these tests, two full thickness cartilage plugs (4 mm diam.) were harvested from the most arthritic area of the tibial plateau, rinsed in PBS, and microtomed on the bony side to produce ~2 mm thick plug with a bottom surface parallel to the intact articular surface. Each plug was tested in reciprocating translation (±1 mm/s) against a flat glass slide, under a constant load (6.27 N) for 3600 s, producing a contact stress of ~0.5 MPa; to minimize wear damage[28], the lag time between alternate reciprocating cycles was increased logarithmically. One plug was tested in a bath of PBS + PI (SCA−PBS) and the neighboring plug in a bath of SF (SCA−SF). As shown previously[11,14,18], the SCA test produces a monotonic rise in the friction coefficient, from a minimum value μ_{min} to a near-equilibrium value μ_{eq}.

MECHANICAL TESTING

After friction testing, each cartilage plug was subjected to unconfined compression stress-relaxation, using a previously described custom apparatus[29]. The samples were subjected to a 5% tare strain for 15 min, followed by two consecutive applications of 10% strain, each maintained over 1 h. A linear regression analysis on the three equilibrium engineering stress and strain values was used to evaluate the equilibrium Young's modulus E_Y. Following these tests, specimens were allowed to recover in a PBS bath and stored at −20°C for subsequent biochemical analyses.

BIOCHEMICAL ANALYSES

The water content of the tested cartilage plugs was determined by lyophilization. Following a 6 h papain digestion (Sigma, St. Louis, MO), the glycosaminoglycan (GAG) content was quantified using a 1,9-dimethylmethylene blue assay, with chondroitin-6-sulfate (Sigma, St. Louis, MO) used as the standard[30]. The total hydroxyproline (OHP) content was determined using a colorimetric method[31], and converted into total collagen content using a mass ratio of collagen to OHP of 7.25[32,33].

STATISTICAL ANALYSES

Samples were pooled into two groups, 'less-OA' and 'more-OA', according to four different criteria: 1) Visual staging (stages ≤ 2 vs stages > 2); 2) equilibrium Young's modulus (samples above the median value of E_Y vs samples below the median value); 3) glycosaminoglycan content (samples above the median value of GAG vs samples below the median); and 4) OHP content (samples above the median value of OHP vs samples below the median value). While visual staging is considered to be an absolute scale (less-OA = normal to mild OA, more-OA = moderate to advanced OA), the remaining three criteria are relative scales which rely on the fact that cartilage plugs were harvested from approximately the same region of the joint, so that sample-to-sample differences in mechanical and biochemical properties may be attributed mostly to the degree of cartilage degeneration.

For each criterion, a two-way analysis of variance (ANOVA) for the factors of OA stage (less-OA vs more-OA) and lubricant (PBS vs SF) was performed to compare the friction coefficients (μ_{MCA}, μ_{min} and μ_{eq}); type I error

Table III
Mean ± standard deviation of the friction coefficient, for the two OA conditions (less-OA vs more-OA, based on four different criteria) and the two lubricants (PBS vs SF). Statistical differences are summarized in Table IV

OA criterion		Friction coefficient	Lubricant	
			PBS	SF
Visual stage	Less-OA	μ_{MCA}	0.026 ± 0.009	0.020 ± 0.070
		μ_{min}	0.036 ± 0.030	0.005 ± 0.002
		μ_{eq}	0.134 ± 0.034	0.040 ± 0.018
	More-OA	μ_{MCA}	0.024 ± 0.009	0.019 ± 0.010
		μ_{min}	0.018 ± 0.012	0.006 ± 0.002
		μ_{eq}	0.106 ± 0.053	0.042 ± 0.015
Modulus	Less-OA	μ_{MCA}	0.028 ± 0.009	0.022 ± 0.007
		μ_{min}	0.028 ± 0.020	0.006 ± 0.001
		μ_{eq}	0.144 ± 0.033	0.037 ± 0.010
	More-OA	μ_{MCA}	0.023 ± 0.008	0.023 ± 0.007
		μ_{min}	0.030 ± 0.033	0.006 ± 0.001
		μ_{eq}	0.100 ± 0.063	0.036 ± 0.080
GAG content	Less-OA	μ_{MCA}	0.027 ± 0.009	0.022 ± 0.005
		μ_{min}	0.030 ± 0.032	0.007 ± 0.002
		μ_{eq}	0.106 ± 0.055	0.040 ± 0.016
	More-OA	μ_{MCA}	0.024 ± 0.010	0.017 ± 0.011
		μ_{min}	0.024 ± 0.015	0.005 ± 0.001
		μ_{eq}	0.119 ± 0.055	0.037 ± 0.012
Collagen content	Less-OA	μ_{MCA}	0.029 ± 0.009	0.022 ± 0.009
		μ_{min}	0.031 ± 0.032	0.007 ± 0.023
		μ_{eq}	0.088 ± 0.045	0.044 ± 0.014
	More-OA	μ_{MCA}	0.022 ± 0.009	0.018 ± 0.008
		μ_{min}	0.025 ± 0.016	0.005 ± 0.001
		μ_{eq}	0.136 ± 0.052	0.033 ± 0.012

probability was set to $\alpha = 0.05$ and significance was set at $P \leq 0.05$. When applicable, *post-hoc* testing of the means was performed with Bonferroni correction.

Results

Seven tibiofemoral specimens were considered to have a visual stage of OA less than or equal to 2 (less-OA), and the remaining nine had a stage between 2 and 3 (more-OA) (Fig. 1); no specimen was found to have a stage of 4. Measurements of Young's modulus and biochemical composition are reported in Table II; these results are summarized for all specimens, and are also separated across their respective median value that identifies the 'less-OA' and 'more-OA' groups.

Table IV
P-values for statistical comparisons of the friction coefficient for the factors of lubricant (PBS vs SF) and OA stage (less-OA vs more-OA, according to four criteria). Bold font is used when $p \leq 0.05$*, indicating significant differences. Differences are observed primarily between PBS and SF*

OA criterion		Effect of lubricant	Effect of OA	Cross effects
Visual stage	μ_{MCA}	**0.0217**	0.699	0.914
	μ_{min}	**0.0011**	0.181	0.081
	μ_{eq}	**0.0011**	0.181	0.814
Modulus	μ_{MCA}	0.1013	0.600	0.096
	μ_{min}	**0.0244**	0.869	0.931
	μ_{eq}	**0.0004**	0.212	0.202
GAG content	μ_{MCA}	0.0643	0.617	0.269
	μ_{min}	**0.0073**	0.605	0.780
	μ_{eq}	**0.0002**	0.288	0.479
Collagen content	μ_{MCA}	**0.0485**	0.295	0.494
	μ_{min}	**0.0093**	0.439	0.320
	μ_{eq}	**0.0003**	0.740	0.593

When the tibiofemoral joint was tested in the MCA configuration, the trend for the time variation of the friction coefficient was the same for all the groups. After an initial small decrease, the friction coefficient remained nearly constant for the duration of the test (Fig. 2), yielding the value of μ_{MCA}. When the tibial plateau cartilage plugs were tested in the SCA configuration, the initial value of the friction coefficient was found to be its minimum value μ_{min}, while the final value was taken as an approximation to the equilibrium value μ_{eq} (Fig. 3).

Means and standard deviations of μ_{MCA}, μ_{min} and μ_{eq} are summarized in Table III, as a function OA stage and lubricant. The *P*-value for statistical differences between less-OA vs more-OA, PBS vs SF, and cross effects are summarized in Table IV. In all but two cases (μ_{MCA} in the OA staging by modulus and by GAG content), it was found that the friction coefficient was statistically smaller in SF than PBS; there were no statistical differences between less-OA and more-OA specimens. Similarly, there were no statistically significant cross effects.

Discussion

The first hypothesis of this study was that the natural progression of OA in human joints leads to an increase in the friction coefficient. The corollary hypothesis was that healthy SF may help mitigate this increase in the friction coefficient. Based on the statistical findings (Table IV), no increase was observed with increasing OA in any of the measures of the friction coefficient (μ_{MCA}, μ_{min}, μ_{eq}); therefore, we must reject the main hypothesis. In a strict sense, since increasing OA did not produce a higher friction coefficient, the opportunity to observe a mitigation of this putative increase with healthy SF did not present itself; consequently, the corollary hypothesis must also be rejected.

A careful examination of the results (Figs. 2 and 3, Table III) suggests that there is not even a trend of increasing friction coefficient with OA, regardless of the criterion employed to assess the degree of degeneration. Four different criteria were employed to assess the absolute or relative stage of OA, based on visual staging (Table I), mechanical properties, and biochemical composition (Table II). These various criteria were employed to complement each other, since the degree of joint degeneration from visual staging alone may be subjective. The consistency of outcomes across all four criteria helps to alleviate any ambiguity that might have arisen from a single criterion. Though additional assessments of degeneration, such as histopathological measures[34], could have been included, the consistency in the observed outcome does not provide a compelling argument for them.

Results do confirm earlier literature findings that healthy SF lubricates cartilage better than PBS[12,15,17,18], presumably due to the presence of various boundary lubricants in the SF[7,16,35–39]. The current study extends this finding to OA joints as well; here, SF reduced μ_{eq} by a factor of ~3, relative to PBS, when examining averages over all specimens (Table III). This reduction can be attributed to the role of boundary lubricants, since the equilibrium response is achieved when interstitial fluid pressurization has subsided[18]. Recent studies have indicated that SF from ACL-deficient joints has a relatively lower concentration of the boundary lubricant lubricin relative to healthy joints[24,25]; a decrease in lubricin was also observed in an animal model of arthritis[5]; similarly, SF from OA joints has been shown to have a lower concentration of surface-active

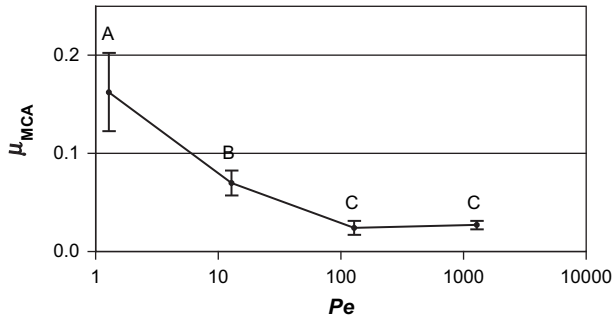

Fig. 4. Friction coefficient μ_{MCA} in a MCA configuration, vs the Peclet number, in immature bovine joints (reproduced from Caligaris M, Ateshian GA. Osteoarthritis Cartilage 2008, with permission). Statistically significant differences are represented by different letters appearing over the data points.

phospholipids[23]. Were the PBS solution used in the current study considered a worst-case scenario of a boundary-lubricant-deficient SF, the observation that healthy SF reduces the friction coefficient of human OA joints relative to PBS is an encouraging outcome. It suggests that intra-articular injections of a SF-like lubricant may produce a statistically significant decrease in the friction coefficient.

To explain the lack of increase in μ_{MCA} with increasing OA (in either lubricant), we must examine the influence of OA on the mechanism of interstitial fluid pressurization, since the value of μ_{MCA} is significantly regulated by this factor[18]. In earlier experimental studies we demonstrated that the friction coefficient decreases with increasing interstitial fluid pressurization[3,13,14,28,40]. According to theory, a MCA promotes higher interstitial fluid pressurization if the migration speed is far in excess of the characteristic diffusive velocity of interstitial fluid inside the cartilage matrix[26]. The physical explanation is that the interstitial fluid pressure in the loaded region of the cartilage layer has little time to subside if the load causing the pressurization moves over that region much faster than the time needed for the pressurized fluid to flow out of that region. From theory, this ratio of migration speed to characteristic fluid flow velocity can be represented by the dimensionless Peclet number, $P_e = V \cdot h / H_A k$, where V is the migration speed, h is a characteristic dimension (such as the cartilage layer thickness or a representative size of the contact region), H_A is the equilibrium aggregate modulus and k the hydraulic permeability of cartilage. In a recent study[18], we verified experimentally that μ_{MCA} decreases significantly with increasing P_e (Fig. 4), consistent with theory.

Studies have shown that H_A decreases while k increases with OA[41], implying that the product $H_A k$ may either increase or decrease with disease, depending on the magnitude of changes in H_A and k. Thus, our earlier enzymatic degradation studies of bovine cartilage, which showed a decrease in interstitial fluid pressurization and increase in friction coefficient[3,19], may have decreased the Peclet number closer to unity. In contrast the current study, which shows no increase in μ_{MCA} with OA, suggests that the natural progression of OA in the human tibiofemoral joint may have left the Peclet number sufficiently greater than unity to cause no detectable change in the friction coefficient (Fig. 4). An estimate of the Peclet number, using the values of H_A reported in Table III, $k \approx 3.5 \times 10^{-4}$ mm^4/N s based on literature reports for normal human femoral condyle cartilage[42,43], with $h \approx 2$ mm and $V = 1$ mm/s as used in this study, yields $P_e \approx 5100$ for less-OA and $P_e \approx 24{,}000$ for more-OA joints. If k is estimated instead to be ten times higher in more-OA joints, then $P_e \approx 2{,}400$. All of these values are significantly greater than unity, providing a comparably low friction coefficient according to the data of Fig. 4. Similarly, changes in H_A and k resulting from the nonlinear response of cartilage with increasing contact stresses are not likely to reduce P_e significantly.

These findings suggest that cartilage from human joints with visual OA stages 1 to 3 maintains sufficiently functional properties to promote the interstitial fluid pressurization necessary to produce a low friction coefficient. The friction coefficients observed here are very similar to our earlier results with healthy immature bovine knee joints[18] (Fig. 4, with $P_e \sim 100-1000$), suggesting that cartilage functional properties are remarkably resilient to OA degradation from visual stages 1 to 3, an observation consistent with the relatively slow progression of this disease.

It is important to keep in perspective that visual stages of OA assessed from dissections typically overestimate radiographic stages of OA. In particular, no joints tested in this study exhibited eburnated or even exposed bone, as would be expected in advanced radiographic staging of OA. For such joints, it may still be reasonably expected that the friction coefficient of bone rubbing against bone would be significantly greater than OA cartilage against OA cartilage. Therefore the main conclusions of this study should be viewed as valid only for the specific range of degeneration observed in the specimen sample tested here.

A potential limitation of this study is the relatively low value of the applied contact load and resulting contact stresses, imposed by limitations on the multi-axial load cell used here. However, prior literature studies have shown that the temporal response of the friction coefficient remains qualitatively similar at higher loads and contact stresses[12,44], while the actual value of the friction coefficient decreases with increasing load[44,45]. On this basis, it is reasonable to expect that the current findings will remain true at higher loads, though this may need to be verified directly. Another potential limitation is the use of bovine SF instead of human SF, to ensure plentiful supply of healthy samples. However, Swann *et al.* have shown that there are no differences in the frictional response of cartilage when using healthy bovine vs healthy human SF[46].

In summary, this study demonstrates that the friction coefficient of human tibiofemoral articular cartilage does not increase with naturally increasing OA, for visual stages ranging from 1 to 3. Though this outcome appears counter-intuitive relative to prior studies of enzymatically or mechanically degraded cartilage, it can be explained by the fact that interstitial fluid pressurization is not necessarily defeated by advancing tissue degeneration. This study also demonstrates that healthy SF decreases the friction coefficient of the osteoarthritic tibiofemoral joint, relative to PBS. Were PBS considered reasonably representative of lubricant-deficient osteoarthritic SF, this outcome suggests that intra-articular injections of a healthy SF-like lubricant, which contains the essential boundary lubricating molecules of native SF, may produce a statistically significant decrease in the cartilage friction coefficient.

Conflict of interest

There is no conflict of interest with regard to the studies reported in this paper.

Acknowledgments

This study was supported with funds from the U.S. National Institutes of Health (NIAMS AR43628).

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